are disclosed, for example, by Ausubel at pp. 2.11.1-2.12.5. Also, see generally Eckstein et al. (ed.), OLIGONUCLEOTIDES AND ANALOGUES: A PRACTICAL APPROACH (IRL Press 1992).

26 DNA sequences encoding a heterologous signal peptide are subcloned in frame with DNA sequences encoding the N-terminus of an HGF variant of the present invention, while DNA sequences encoding the HGF variant are subcloned in frame with the N-terminus of the antibody portion of the fusion protein. Subcloning is performed in accordance with conventional techniques, such as the use of restriction enzyme digestion to provide appropriate termini, the use of alkaline phosphatase treatment to avoid undesirable joining of DNA molecules, and ligation with appropriate ligases. Techniques for such manipulation are described by Sambrook and Ausubel, and are well-known in the art. Techniques for amplification of cloned DNA in bacterial hosts and isolation of cloned DNA from bacterial hosts also are well-known. Id.

27 The cloned fusion protein is cleaved from the cloning vector and inserted into an expression vector. Suitable expression vectors typically contain (1) prokaryotic DNA elements coding for a bacterial replication origin and an antibiotic resistance marker to provide for the growth and selection of the expression vector in a bacterial host; (2) eukaryotic DNA elements that control initiation of transcription, such as a promoter; and (3) DNA elements that control the processing of transcripts, such as a transcription termination/polyadenylation sequence.

28 A fusion protein of the present invention is expressed in either eukaryotic or prokaryotic cells. Suitable prokaryotic expression systems are described in Example 9, below. E. coli and B. subtilis are examples of two suitable prokaryotic host cells. Prokaryotic expression of fusion proteins, in accordance with the invention, would increase solubility of the expressed product, would facilitate purification and favor secretion.

29 However, preferably the fusion protein of the present invention is expressed in eukaryotic cells, such as mammalian, insect and yeast cells. Mammalian cells are especially preferred eukaryotic hosts because mammalian cells provide suitable post-translational modifications such as glycosylation. Examples of mammalian host cells include Chinese hamster ovary cells (CHO-K1; ATCC CCL61), rat pituitary cells (GH.sub.1 ; ATCC CCL82), HeLa S3 cells (ATCC CCL2.2), rat hepatoma cells (H-4-II-E; ATCC CRL1548) SV40-transformed monkey kidney cells (COS-1; ATCC CRL 1650) and murine embryonic cells (NIH/3T3; ATCC CRL 1658). Preferably, the mammalian host cells are NIH-3T3 cells.

30 For a mammalian host, the transcriptional and translational regulatory signals may be derived from viral sources, such as adenovirus, bovine papilloma virus, simian virus, or the like, in which the regulatory signals are associated with a particular gene which has a high level of expression. Suitable transcriptional and translational regulatory sequences also can be obtained from mammalian genes, such as actin, collagen, myosin, and metallothionein genes.

31 Transcriptional regulatory sequences include a promoter region sufficient to direct the initiation of RNA synthesis. Suitable eukaryotic promoters include the promoter of the mouse metallothionein I gene (Hamer et al., J. Molec. Appl. Genet. 1: 273 (1982)); the TK promoter of Herpes virus (McKnight, Cell 31: 355 (1982)); the SV40 early promoter (Benoist et al., Nature 290: 304 (1981)); the Rous sarcoma virus promoter (Gorman et al., Proc. Nat'l Acad. Sci. USA 79: 6777 (1982)); and the cytomegalovirus promoter (Foecking et al., Gene 45: 101 (1980)).

Invitrogen (San Diego, Calif.), and the American Type Culture Collection (Rockville, Md.).

19 As noted above, the DNA sequence encoding the Ig portion of a fusion protein within the present invention preferably encodes an Ig heavy chain. More preferably, such a DNA sequence encodes the hinge, CH.sub.2 and CH.sub.3 domains of IgG. Immunoglobulin DNA sequences can be obtained using the polymerase chain reaction (PCR) as described, for example, by Coligan et al. (eds.), CURRENT PROTOCOLS IN IMMUNOLOGY, pages 10.20.1-10.20.8 (Wiley Interscience 1992) (hereafter "Coligan").

20 By one approach, antibody DNA sequences are amplified from RNA of cells that synthesize an immunoglobulin. Larrick et al., "PCR Amplification of Antibody Genes," in 2 METHODS: A COMPANION TO METHODS IN ENZYMOLOGY 106 (1991). Briefly, total RNA is isolated from immunoglobulin-producing cells using standard techniques. See Ausubel at pages 4.1.2-4.2.8. Poly A+ RNA then is isolated from total RNA using the standard technique of oligo-dT column chromatography as described, for instance, by Sambrook. Single-stranded cDNA molecules then are synthesized from poly A+ RNA using reverse transcriptase. Techniques for synthesizing cDNA are described in each of Sambrook, Ausubel, and Coligan. Moreover, commercially available kits can be used to synthesize cDNA molecules. For example, such kits are available from GIBCO/BRL (Gaithersburg, Md.), Clontech Laboratories, Inc. (Palo Alto, Calif.), Promega Corporation (Madison, Wis.) and Stratagene Cloning Systems (La Jolla, Calif.).

21 The PCR reaction is performed with the single-stranded cDNA template and a mixture of oligonucleotide primers. The design of oligonucleotide primers can be based upon the DNA sequence of the immunoglobulin of interest. Alternatively, oligonucleotide primers can be designed based on information from a database of immunoglobulin amino sequences, such as Kabat et al., SEQUENCES OF PROTEINS OF IMMUNOLOGICAL INTEREST, U.S. Department of Health and Human Services (1983), taking into account degeneracies for each amino acid. Oligonucleotide synthesis and purification techniques are described in Sambrook and Ausubel, respectively. The PCR procedure is performed via well-known methodology. See, for example, Ausubel, Coligan, and Bangham, "The Polymerase Chain Reaction: Getting Started," in PROTOCOLS IN HUMAN MOLECULAR GENETICS (Humana Press 1991). Moreover, PCR kits can be purchased from companies such as Stratagene Cloning Systems (La Jolla, Calif.) and Invitrogen (San Diego, Calif.).

22 Alternatively, immunoglobulin-encoding DNA sequences can be synthesized using PCR with cloned immunoglobulins. DNA sequences encoding HGF/NK1 or HGF/NK2 can be synthesized using PCR with RNA isolated from cells that produce such variants.

23 Alternatively, DNA sequences encoding HGF/NK1 or HGF/NK2 can be obtained using PCR with an HGF/NK1 or HGF/NK2 cDNA template.

24 DNA sequences that encode heterologous signal peptides can be obtained via PCR with RNA isolated from cells that produce the HGF variants of the present invention. Such DNA sequences also can be obtained by isolating fragments of HGF/NK1 or HGF/NK2 cDNAs that encode a signal peptide.

25 Alternatively, DNA sequences encoding signal peptides can be obtained by synthesizing oligonucleotides that encode known signal peptide amino acid sequences. Such amino acid sequences are disclosed, for example, by Darnell et al., supra, and Wallis et al., THE BIOCHEMISTRY OF THE POLYPEPTIDE HORMONES, page 212 (John Wiley & Sons 1985). Techniques for oligonucleotide synthesis